ABSTRACT OF THE DISCLOSURE

Site-specific recombinases provide a means of efficiently manipulating chromosomal sequences in mammalian cells in culture and in animals ~~mice~~. Embryonic stem cells containing recombinase nucleic acid constructs that were expressed in the male germline ~~would~~ simplify current protocols for producing mice bearing homologously recombined alleles that have been secondarily rearranged by a site-specific recombinase. Five lines of transgenic mice containing a fusion gene consisting of the mouse protamine 1 gene promoter and the Cre recombinase coding sequence (ProCre nucleic acid constructs) showed high levels of Cre-mediated recombination in the germline, but did not show appreciable recomb~~ination in other tissues~~. In different ProCre strains, between 80% and 100% of the progeny that inherited a Cre target nucleic acid construct from males that were also heterozygous for a ProCre nucleic acid construct inherited the Cre-recombined target. ProCre nucleic acid constructs and recombined targets segregated in the first generation. When ES cells prepared from one ProCre line were transfected with vectors containing a loxP-flanked neomycin cassette, G418 resistant, homologously recombined clones, in which the loxP sites remained functional, were readily isolated. These data establish that ProCre nucleic acid constructs will facilitate the production of subtle, conditional, or tissue-specific mutations in mice as well as the production and analysis of mice with recombinase-conditional lethal alleles.